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Review Article

Critical Appraisal of Gefitinib in the Treatment of Non-Small Cell Lung Cancer

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Abstract.

The leading cause of death from malignant tumors worldwide is lung cancer. Before the development of molecularly targeted therapy, chemotherapy with platinum-based doublets was considered as the standard first-line treatment in advanced non-small cell lung cancer (NSCLC) patients. The introduction of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) has led to remarkable advances in the treatment of NSCLC. Two activating *EGFR* mutations (Exon 19 deletion and Exon 21 L858R mutation) have been correlated with dramatic responses to EGFR-TKI. Every effort should be made to identify the *EGFR* mutation status in NSCLC patients prior to the initial systemic treatment in order to select those who are most likely to benefit from EGFR-TKIs. At the present time, first-generation EGFR-TKIs are available for clinical use, including gefitinib and erlotinib. Gefitinib was the first drug developed as an EGFR-TKI for NSCLC treatment. Several randomized phase III studies revealed that gefitinib provided superior response rate, improved PFS, and less toxicity compared with doublet chemotherapy for advanced NSCLC with activating EGFR mutation. Currently, first-line treatment with gefitinib is used in metastatic NSCLC patients with tumor *EGFR* mutation. Gefitinib is also administered as salvage therapy for NSCLC patients previously treated with chemotherapy. The standard of care for previously untreated patients with *EGFR* mutation-negative or unknown status still remains platinum-based chemotherapy. In this article, we have reviewed the relevant clinical data regarding gefitinib as a molecularly targeted therapy for NSCLC.

Keywords **:** gefitinib, non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor

綜合評論

Gefitinib 於非小細胞肺癌治療之關鍵評論

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中文摘要

肺癌為全世界惡性腫瘤死亡率最高之癌症。在分子標靶治療發展出來以前，以 platinum 為主的合併化學藥物治療(doublets)是晚期非小細胞肺癌的第一線標準治療。自從有了上皮細胞生長因素接收器-酪胺酸酶抑制劑(epidermal growth factor receptor-tyrosine kinase inhibitor，EGFR-TKI)之後，非小細胞肺癌的治療便有了長足之進展。*EGFR* 基因有 exon 19 突變(deletion)，或 exon 21 突變(L858R point mutation)之患者對 EGFR-TKI 的藥效反應相當地好。所以對於每一位非小細胞肺癌的患者，臨床醫師應該要盡力去檢測出患者的 *EGFR* 基因之突變狀態，以找出適合 EGFR-TKI 治療之病人。第一代的 EGFR-TKIs，包括 gefitinib 與 erlotinib。Gefitinib 是第一個發展出來治療非小細胞肺癌的 EGFR-TKI。一些隨機分配之第三期臨床試驗顯示，gefitinib 與合併化學藥物治療相比之下，對於有 *EGFR* 基因活化性突變的晚期非小細胞肺癌，具有較好的藥效反應、較好的無疾病惡化存活期、及較少的副作用。目前，gefitinib 是具有 *EGFR* 基因突變的晚期非小細胞肺癌之第一線治療藥物。Gefitinib 也可作為接受過化學治療的非小細胞肺癌患者之挽救性治療。對於野生型 *EGFR* 之患者，或者是 *EGFR* 基因突變狀態不明之患者，以 platinum 為主的合併化學藥物治療仍然是第一線標準治療。本篇文章回顧了 Gefitinib 作為分子標靶治療之相關臨床研究。

***關鍵字*:** gefitinib、非小細胞肺癌、上皮細胞生長因素接收器、酪胺酸酶抑制劑

INTRODUCTION

Lung cancer is the leading cause of death worldwide arising from malignant tumors. Only approximately 15% of all lung cancer patients survived for 5 years or more after diagnosis. More than 85% of lung cancer cases have the non-small cell lung cancer (NSCLC) subtype; most patients present with advanced lung cancer and their 2-year survival rate is only 10-15% [1,2]. Before the development of molecularly targeted therapy, chemotherapy with platinum-based doublets was considered as the standard first-line treatment for advanced NSCLC. Chemotherapy has provided modest improvements in patient survival, but lung cancer patients generally still have a dismal prognosis. Considering the relative non-specificity and toxicity of chemotherapy, the development of novel therapeutic strategies is imperative. Over the last decade, molecularly targeted therapies such as gefitinib or erlotinib for NSCLC treatment have demonstrated remarkable advances, including improved progression-free survival (PFS), overall survival (OS), and superior quality of life in certain patient populations [3-7].

The identification of several driver oncogenes related to tumor progression and lung cancer metastasis has resulted in the detection of several potential therapeutic targets [2,3,6]. The first oncogenic driver mutation emerged in 2004 with the detection of activating mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR). The frequency of *EGFR* mutations in NSCLC patients has been reported to be approximately 5-30%, depending on the different population [8-11]. It was observed that a higher incidence of *EGFR* mutations was detected in East Asians [12,13]. These mutations were identified predominantly in pulmonary adenocarcinomas. EGFR and its downstream signaling pathway have been extensively studied in recent years. Two activating *EGFR* mutations (Exon 19 deletion and Exon 21 L858R point mutation) have been associated with dramatic responses to EGFR tyrosine kinase inhibitors

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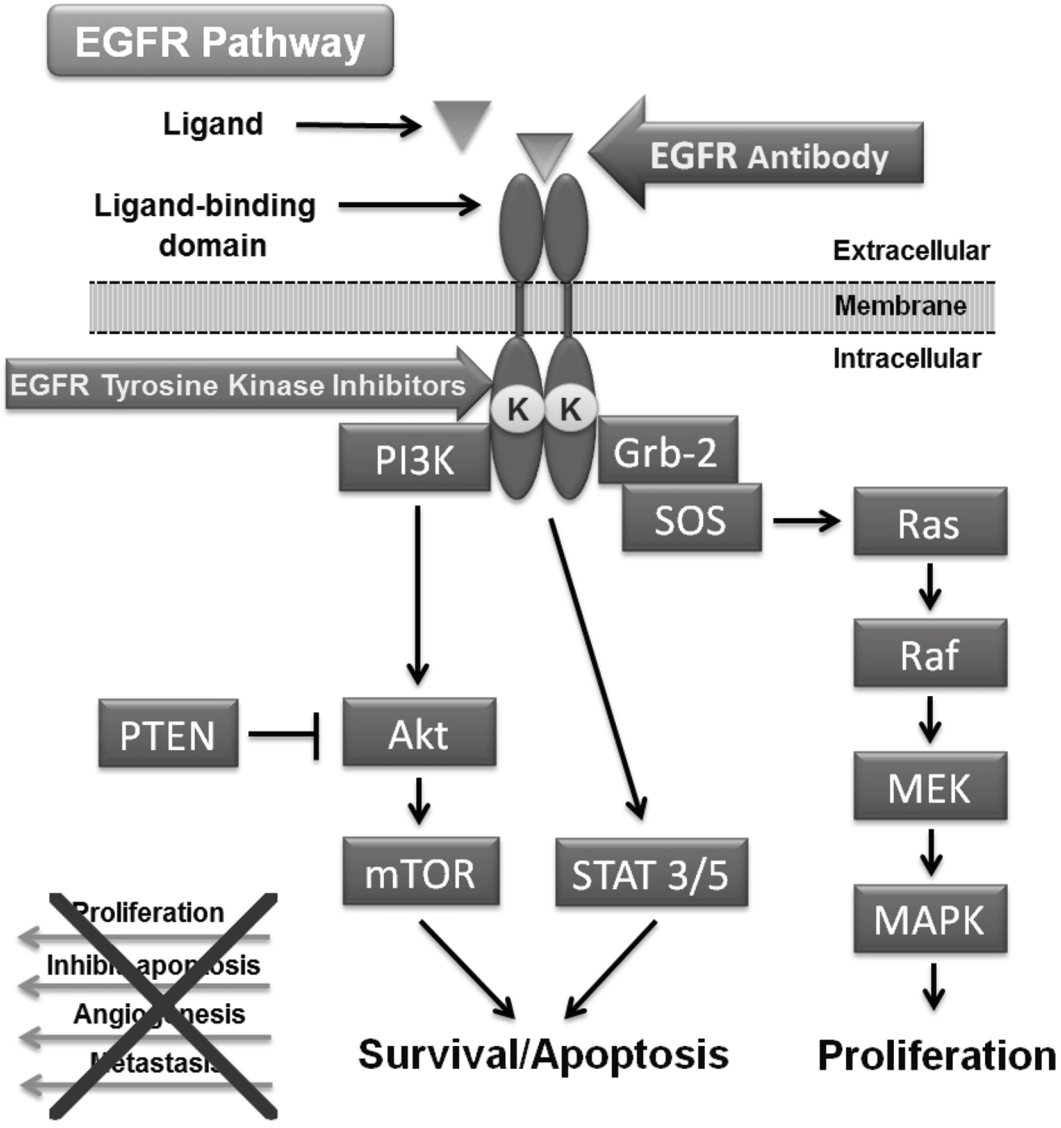

Figure 1. EGFR signal transduction pathway. The reactions of ligand-receptor and receptor-receptor interactions activate intracellular signaling pathways that regulate cellular survival/apoptosis, proliferation, and other cellular functions that lead to the activation of malignant behaviors. EGFR monoclonal antibody binds to EGFR and interferes with the binding of ligands (such as EGF). EGFR-TKIs (e.g. gefitinib) bind to the intracellular tyrosine kinase domain and inhibit signal transduction pathway. EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor

(TKI), such as gefitinib or erlotinib [9,10,14]. They exhibited favorable toxicity profiles and convenience for use. Gefitinib was the first drug developed as an EGFR-TKI for NCSLC treatment [15]. The relevant clinical information regarding gefitinib as a molecularly targeted therapy for NSCLC was reviewed in this article.

SIGNAL TRANSDUCTION PATHWAY OF EGFR

Epidermal growth factor receptors (EGFR) and ErbB receptors belong to the same subclass I of the receptor tyrosine kinase (TK) superfamily. This ErbB family comprises four structurally similar receptors, including ErbB1 (EGFR/HER1), ErbB2 (HER2/Neu), ErbB3 (HER3), and ErbB4 (HER4) [16,17]. Of these four receptors, EGFR was the first to be identified. These receptors contain an extracellular domain for the binding of ligands, a transmembrane domain, and an intracellular TK domain. The binding of ligands to the extracellular domain of EGFR results in dimerization of two receptor molecules, and activates receptor autophosphorylation through TK activity. Then, autophosphorylation activates several downstream signaling pathways which may lead to tumor proliferation, migration, metastasis, and inhibition of apoptosis [16-18].

The TK family consists of two main intracellular signal transduction pathways. One of them is the Ras-Raf-MEK-MAPK pathway which regulates gene transcription, and proliferation of tumor cells. The other crucial downstream pathway is the phosphatidylinositol 3-kinase (PI3K) -Akt pathway, which activates a series of reactions including cell proliferation, growth, and blocking apoptosis. Another signaling route is through the Janus kinase/signal transducers and activators of transcription (Jak/Stat) pathway [17,18]. When all of the pathways are activated, it may ultimately contribute to various cellular reactions containing cell growth, division, repair, survival (or apoptosis), adhesion, invasion, and metastasis.

EGFR INHIBITION

In 1981, Mendelsohn and colleagues reported that EGFR is often overexpressed in the human cancer cell, and is related to a poor outcome. Thus, they proposed the theory of a targeted cancer therapy through EGFR inhibition [19]. The previous studies reported that the frequency of EGFR overexpression in NSCLC specimens was around 43% to 89% depending on different populations, detection techniques, and the definition of EGFR overexpression [20-24]. However, in these studies, the association between EGFR expression and survival benefit revealed controversial results [24,25].

In these studies, several strategies were applied for targeting the EGFR. Among them, EGFR-TKIs and monoclonal antibodies (MoAbs) were most frequently used in clinical applications [1,2,4,26]. Small molecule TKIs bind to the intracellular TK domain of EGFR and interfere with signal transduction. MoAbs target the extracellular domain of EGFR and interfere with receptor signaling. EGFR-TKIs and MoAbs seem to possess similar effects with regard to receptor-dependent downstream signal transduction pathways, including the MAPK and PI3K-Akt pathways. Both of them lead to the effective inhibition of the major EGFR signaling pathways [27,28]. Therefore, EGFR-TKIs and MoAbs exhibit their anticancer effect in NSCLC patients by blocking several crucial cellular functions regulated by the EGFR, including cell-cycle arrest, cell apoptosis, blockade of cancer cell invasion and metastasis (Figure 1) [27,29,30]. After the discovery of an intimate association between the efficacy of EGFR-TKIs and activating *EGFR* mutations, the EGFR-TKIs as targeted therapies for EGFR-mutant NSCLC have been intensively studied [2-4]. Nevertheless, anti-EGFR monoclonal antibodies (e.g. cetuximab) have been studied less extensively and have demonstrated improved outcomes in merely one randomized phase III study of cetuximab added to doublet chemotherapy for treatment in chemotherapy-naïve NSCLC patients [2-4,31].

FIRST-GENERATION EGFR-TKI

First-generation EGFR-TKIs include gefitinib (Iressa) and erlotinib (Tarceva). Both have been approved for the treatment of advanced NSCLC, and are orally administered small molecules that reversibly inhibit the EGFR tyrosine kinase and interfere with downstream signaling. Their side effects (like dose-

dependent skin rash and diarrhea) are usually mild to moderate, and manageable in the outpatient department under close monitoring. The first drug developed as an EGFR-TKI for NSCLC treatment was gefitinib [2,3,15]. In the phase I trial, gefitinib has demonstrated objective responses in NSCLC patients who were heavily treated with prior extensive rounds of chemotherapy or chemoradiotherapy, when administered as a single agent [32]. Two randomized multicenter phase II studies [Iressa Dose Evaluation in Advanced Lung Cancer 1 (IDEAL 1) and 2 (IDEAL 2)] have been conducted in patients with locally advanced or metastatic NSCLC who had progressive disease after prior chemotherapy, including platinum-based and docetaxel-based therapies in order to evaluate the safety and efficacy of two oral doses of gefitinib (250 and 500 mg/day) [33,34]. In the IDEAL 1 trial, a response rate of 18.7% and remarkably improved disease-related symptoms were demonstrated. Gefitinib at 250 mg/day was as effective as 500 mg/day, and exhibited the superior toxicity profiles [33]. The IDEAL 2 trial revealed 12% objective response rates in the 250 mg/d group, and 9% in the 500 mg/d group. Similar toxicity profiles had been observed in the IDEAL 1 and IDEAL 2 studies [33,34]. Based on these trials, The US Food and Drug Administration (FDA) approved gefitinib as a third-line treatment for locally advanced or metastatic NSCLC patients after failure of platinum- and docetaxel-based chemotherapies in 2003 [18].

The ISEL (Iressa Survival Evaluation in Lung Cancer) trial requested by the US FDA was a randomized phase III study designed to evaluate the survival benefit of gefitinib [35]. In this study, 1692 patients with previously treated advanced NSCLC were randomized to either gefitinib treatment or placebo, and gefitinib did not demonstrate statistically longer survival time compared with the placebo among all patients (median survival: 5.6 vs. 5.1 months; p = 0.087). Nevertheless, preplanned subgroup analyses revealed that Asian patients receiving gefitinib (n = 235) had significantly longer survival as compared with those receiving placebo (n = 107) (median survival: 9.5 vs. 5.5 months; p = 0.01). Significantly longer survival was also observed in patients who never smoked receiving gefitinib (n = 250) than those receiving a placebo (n = 125) (median survival: 8.9 vs. 6.1 months; p = 0.012). In 2005, the US FDA limited the use of gefitinib to patients continuing to derive benefit from gefitinib prescribed previously or those enrolled in the clinical trial, because the lack of survival benefit that was demonstrated in the ISEL study [15,18].

A multicenter phase III randomized trial [Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST)] with a non-inferiority design to compare gefitinib with docetaxel recruited 1433 advanced NSCLC patients receiving at least one line of platinum-based chemotherapy. In this INTEREST trial, the results revealed the non-inferiority of gefitinib over docetaxel in terms of overall survival [median survival: 7.6 vs. 8.0 months; hazard ratio (HR): 1.020; 96% confidence interval (CI): 0.905-1.150], and suggested that gefitinib is an efficacious therapy in previously treated patients with molecularly unselected advanced NSCLC [36].

In the subgroup analyses of the ISEL study described above [35], gefitinib demonstrated significant survival benefits in East Asian patients, and those who had never smoked. Therefore, the Iressa Pan-Asia Study (IPASS) was initiated to evaluate the efficacy of gefitinib in East Asian patients [5]. The IPASS trial was the first randomized phase III trial to compare EGFR-TKI (gefitinib) with doublet chemotherapy (paclitaxel plus carboplatin) as first-line therapy in selected East Asia patients who were former light smokers or non-smokers with advanced pulmonary adenocarcinoma. In this study, 1217 patients were enrolled, and 437 patients (35.9%) received *EGFR* mutation analysis. In a subgroup including 261 cases with *EGFR* mutation positive tumor, patients who received gefitinib had significantly longer progression-free survival (PFS) than those receiving paclitaxel plus

Table 1. Phase III randomized trials comparing first-line EGFR-TKI with chemotherapy in clinically or molecularly selected NSCLC patients with activating *EGFR* mutations

	I-PASS		NEJ002		WJTOG3405		OPTIMAL (CTONG-0802)		EURTAC	
	G	P + Cb (*p**)	G	P + Cb (*p**)	G	D + Cis (*p**)	E	Ge + Cb (*p**)	E	Platinum based (*p*)*
RR (%)	71.2	47.3 (<0.001)	73.7	30.7 (<0.001)	62.1	32.2 (<0.0001)	83	36 (<0.001)	54.5	10.5
CR (%)	NA	NA	4.4	0	NA	NA	2	0	3	0
PFS (mo)	9.5	4.9 (<0.001)	10.8	5.4 (<0.001)	9.2	6.3 (<0.0001)	13.1	4.6 (<0.001)	9.7	5.2 (<0.001)
OS (mo)	21.6	21.9 (0.99)	30.5	23.6 (0.31)	34.8	37.3	22.7	28.8 (0.69)	19.3	19.5 (0.87)

*The *p* values: when comparing with EGFR-TKI group
Cb = carboplatin; Cis = cisplatin; CTONG = Chinese Thoracic Oncology Group; D = docetaxel; E = erlotinib; EGFR = epidermal growth factor receptor; EURTAC = European Tarceva versus chemotherapy; G = gefitinib; Ge = gemcitabine; I-PASS = Iressa Pan Asia study; NA = not applicable; NEJ002 = North East Japan 002; NSCLC = non-small-cell lung cancer; OPTIMAL = Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive NSCLC; OS = overall survival; P = paclitaxel; PFS = progression-free survival; RR = response rate; TKI = tyrosine kinase inhibitor; WJTOG3405 = West Japan thoracic oncology group 3405

carboplatin (HR: 0.48; 95% CI: 0.36-0.64; $p < 0.001$). However, in another subgroup including 176 patients without *EGFR* mutation, PFS was significantly shorter among patients who received gefitinib than those who received paclitaxel plus carboplatin (HR: 2.85; 95% CI: 2.05-3.98; $p < 0.001$).This trial suggested that the existence of tumor *EGFR* mutations is an important predictor of better outcome in patients receiving gefitinib. The importance of identifying the *EGFR* mutation status before deciding on initial treatment was first discovered in the IPASS trial [5,37]. Similar results were further confirmed in other phase III trials that revealed a significantly improved PFS and better quality of life in patients receiving EGFR-TKI as compared with platinum-based doublet chemotherapy (Table 1) [5,38-42]. A phase III randomized trial (WJTOG 3405) of gefitinib compared with cisplatin/docetaxel as first-line treatment for EGFR-mutant NSCLC revealed that gefitinib provided a 3-year survival benefit for EGFR-mutant advanced NSCLC after 5 years of follow-up (median survival: 34.8 vs. 37.3 months; HR: 1.252; 95% CI: 0.883-1.775), although no significant difference in overall survival was observed [38,39].

In 2009, mainly based on results from IPASS and INTEREST trial, the European Medicines Agency (EMA) approved gefitinib as a targeted therapy for locally advanced or metastatic NSCLC harboring activating *EGFR* mutation [43,44]. Gefitinib is also approved for use in Japan, Taiwan, China, Korea, and several Asian countries [18,43].

GEFITINIB COMBINED WITH CHEMOTHERAPY

Previous reports suggest that gefitinib does not induce myelosuppression, which was found in patients receiving conventional chemotherapy [17,32-35]. In order to evaluate whether the addition of EGFR-TKI to chemotherapy can enhance the antitumor effect and provide longer survival than chemotherapy alone, four phase III trials in previously untreated patients with advanced NSCLC were initiated (Table 2) [45-48]. The INTACT (Iressa NSCLC Trial Assessing Combination Treatment) 1 trial enrolled 1093 patients who were randomized to chemotherapy (gemcitabine/cisplatin) with either gefitinib 250 mg/day, gefitinib 500 mg/day, or placebo. No significantly different response rate, time to progression, and overall survival was observed among these treatment groups. The INTACT 2 study with the design similar to INTACT 1 recruited 1037 patients, and the chemotherapy regimen was carboplatin and paclitaxel [46]. The results also showed no significantly different response rate, time to progression, and overall survival among different treatment groups. The addition of Erlotinib to chemotherapy has also been evaluated, like gefitinib. In the TRIBUTE (Tarceva Responses in Conjunction with Paclitaxel and Carboplatin) and TALENT (Tarceva Lung Cancer Investigation) studies, chemotherapy-naïve NSCLC patients received chemotherapy both

Table 2. Four randomized Phase III trials of chemotherapy with or without EGFR-TKI (gefitinib or erlotinib) in clinical or molecularly-unselected patients with treatment-naïve advanced NSCLC (A total of 4361 patients)

Trial	No. of patients	Treatment comparison	Response rate (%)	PFS (mo)	OS (mo)
INTACT 1	1093	Cis + gemcitabine, or with gefitinib (250 or 500 mg/d)	44.8 vs. 50.3 vs. 49.7	6.0 vs. 5.8 vs. 5.5 (p = 0.76)	10.9 vs. 9.9 vs. 9.9 (p = 0.45)
INTACT 2	1037	Cb + paclitaxel, or with geitinib (250 or 500 mg/d)	42 vs. 41 vs. 37	5.0 vs. 5.3 vs. 4.6 (p = 0.562)	9.9 vs. 9.8 vs. 8.7 (p = 0.64)
TRIBUTE	1059	Cb + paclitaxel, or with erlotinib	19.3 vs. 21.5	4.9 vs. 5.1 (p = 0.36)	10.5 vs. 10.6 (p = 0.95)
TALENT	1172	Cis + gemcitabine, or with erlotinib	29.9 vs. 31.5	5.7 vs. 5.5 (p = 0.74)	10.3 vs. 10.0 (p = 0.49)

Cb = carboplatin; Cis = cisplatin; INTACT = Iressa NSCLC Trial Assessing Combination Treatment; NSCLC = non-small-cell lung cancer; PFS = progression-free survival; OS = overall survival; TALENT = Tarceva Lung Cancer Investigation; TKI = tyrosine kinase inhibitor; TRIBUTE = Tarceva Responses in Conjunction with Paclitaxel and Carboplatin

with and without erlotinib [47,48]. These trials also failed to demonstrate improved survival in patients receiving combination therapy with chemotherapy plus erlotinib. The above-mentioned four randomized phase III studies, including 4361 patients with chemo-naïve NSCLC, obviously revealed that the combination of EGFR-TKIs (gefitinib or erlotinib) with chemotherapy does not provide superior survival benefit over chemotherapy alone. Therefore, gefitinib should not be added to cytotoxic chemotherapy as the first-line treatment in molecularly unselected NSCLC patients [2,3].

EGFR MUTATION

Previous studies have demonstrated that *EGFR* mutations may predict treatment response to EGFR-TKIs and also be a prognostic factor [17,47,49-53]. Cappuzzo and colleagues analyzed tumor specimens of NSCLC from 102 patients receiving gefitinib for tumor *EGFR* status by fluorescence *in-situ* hybridization (FISH), and immunohistochemistry, and for *EGFR* mutation by DNA sequencing [49]. The results revealed the tumor *EGFR* status and mutation were correlated with treatment response and patient survival [2,3,49]. *EGFR* mutation status possessed the best correlation with treatment effect [3,9,10,17,54], followed by FISH assay [49,54]. Several large serial studies on the epidemiology of *EGFR* mutation revealed that the reported mutations were all somatic and identified in exons 18, 19, 20, and 21 of the *EGFR* gene encoding partial intracellular TK domain of EGFR [13,55,56]. Prior studies also reported that the sensitivity to EGFR-TKIs was correlated with three kinds of *EGFR* mutations, including (1) in-frame deletions within exon 19, accounting for approximately 46% of all EGFR mutations (the most common EGFR mutations); (2) missense mutations within exon 18, 20, or 21, accounting for approximately 41% of all mutations (the second most common EGFR mutations), especially L858R point mutations within exon 21; and (3) in-frame duplications and/or insertions within exon 20 (approximately 5% of all mutations) [2,13,55]. In addition to *EGFR* mutations, East Asian descent, female sex, never-smoker, and adenocarcinoma histology have also been reported to have a correlation with sensitivity to EGFR-TKIs. Another large study that enrolled 12,244 patients revealed that the most common mutations were exon 19 mutation (50%), followed by exon 21 (40%), exon 20 (6%), and exon 18 (4%) mutations. L858R in exon 21 and deletion of E746-A750 in exon 19 accounted for approximately 33% and 24% of all mutations [56]. An obvious correlation between the response to EGFR-TKIs and EGFR mutations has been reported. The best response rate (around 70%) was demonstrated in NSCLC patients with exon 19 mutations, followed by those with exon 21, 18, and 20 mutations (approximately 20% or slightly higher). EGFR-mutant NSCLC patients receiving EGFR-TKI

Table 3. Six phase III trials of maintenance therapy with EGFR-TKIs after first line chemotherapy (A total of 3006 patients)

Trial	No. of patients	Maintenance treatment	Median PFS	*p*-value	Median OS (mo)	*p*-value
WJTOG 0203	595	Gefitinib vs. observation	4.6 vs. 4.3 months	<0.001	13.7 vs. 12.9	0.11
EORTC 08021-ILCP 01/03	173	Gefitinib vs. placebo	4.1 vs. 2.9 months	0.002	10.9 vs. 9.4	0.204
INFORM	296	Gefitinib vs. placebo	4.8 vs. 2.6 months	<0.0001	18.7 vs. 16.9	0.26
SATURN	889	Erlotinib vs. placebo	12.3 vs. 11.1 weeks	<0.0001	12 vs. 11	0.0088
ATLAS	743	Bevacizumab + erlotinib vs. Bevacizumab + placebo	4.8 vs. 3.7 months	0.001	14.4 vs. 13.3	0.5604
IFCT-GFPC 0502[a]	310	Erlotinib vs. observation	2.9 vs. 1.9 months	0.003	11.4 vs. 10.8	0.3043

Abbreviations: ATLAS =Avastin Tarceva Lung Adenocarcinoma Study; EGFR = epidermal growth factor receptor; EORTC = European Organization for Research and Treatment of Cancer; IFCT-GFPC = Intergroupe Francophone de Cancerologie Thoracique–Groupe Francais de Pneumo-Cancerologie; ILCP = Italian Lung Cancer Project; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor; SATURN = Sequential Tarceva in Unresectable Non–Small-Cell Lung Cancer; WJTOG = West Japan Thoracic Oncology Group

[a]IFCT-GFPC 0502 was a trial with 3 arms, including maintenance gemcitabine, maintenance erlotinib, and observation group

had median PFS of about 10 months. The PFS varied widely because of several potential mechanisms, including T790M mutation, BIM polymorphism, c-Met amplification, and alterations within chromosome 7p, and even the percentage of *EGFR* mutation-negative cancer cells [2-4,57-62].

Several methods are utilized to identify *EGFR* mutations in tumor specimens from lung cancer patients, including direct sequencing, Scorpion ARMS (amplified refractory mutation system), and PNA-LNA (peptide nucleic acid-locked nucleic acid) PCR (polymerase chain reaction) clamp techniques [5, 63-66]. The sensitivity of direct sequencing is relatively low and it needs a higher percentage of mutant DNA in order to detect *EGFR* mutations in tumor specimens (10-25% mutant DNA). Therefore, objective response rates of 10-20% or higher in particular clinical populations receiving EGFR-TKI were reported in *EGFR* wild type NSCLC patients whose *EGFR* mutation status was detected by the direct DNA sequencing method [67-69]. High-sensitivity methods, including Scorpion ARMS and PNA-LNA PCR clamp techniques, are capable of detecting ≥1% mutant DNA [5,63-65]. However, the Scorpion ARMS and PNA-LNA PCR clamp techniques are only able to identify recognized mutations, but direct sequencing is capable of detecting new mutations [63-66]. Tumor specimens used for *EGFR* mutation assessment are commonly collected from biopsies in the detected pulmonary or metastatic tumors. Specimens obtained from pleural effusion, plasma-free DNA, and circulating tumor cells may also be utilized for *EGFR* mutation assessment [63,64,66,70-73].

FIRST-LINE GEFITINIB TREATMENT FOR EGFR-MUTANT NSCLC

First-line treatment with EGFR-TKIs for EGFR -mutant NSCLC has demonstrated improved PFS, better quality of life, and less treatment-related toxicity compared with platinum-based doublet chemotherapy in several recent randomized phase III studies (Table 1) [5,38-42]. Thus, *EGFR* mutation analysis for advanced NSCLC patients being considered for first-line EGFR-TKI should be performed, and gefitinib as first-line treatment is recommended for NSCLC patients with activating *EGFR* mutation [74]. EGFR-mutant NSCLC patients receiving EGFR-TKI had median PFS of around 10 months. When first-line platinum-based doublet chemotherapy was used for EGFR-mutant NSCLC, the median PFS was only 5-6 months. However, no significant difference in overall survival was found between EGFR-mutant patients receiving EGFR-TKI and those receiving first-line chemotherapy [41,75-78]. In patients with *EGFR* mutation-negative or unknown status, first-line treatment

with chemotherapy is preferred. First-line EGFR-TKIs in NSCLC patients with *EGFR* mutation-negative or unknown status might have a detrimental effect on PFS and OS [5,79,80].

In spite of the initial successful treatment with gefitinib in EGFR-mutant NSCLC patients, most of them will eventually experience progressive disease (acquired resistance to gefitinib) [81]. Strategies for overcoming acquired resistance to gefitinib are being developed [2,3,57]. At the present time, a number of treatment choices are available after failure of gefitinib treatment, such as salvage chemotherapy, use of another approved EGFR-TKI, participating in clinical studies with second-line molecularly targeted therapy, or chemotherapy with continuation of the EGFR-TKI already initiated. Of the above-mentioned therapeutic choices, only salvage chemotherapy is regarded as a standard of care or a preferred option after failure of gefitinib [2-4].

GEFITINIB AS MAINTENANCE TREATMENT AFTER FIRST-LINE CHEMOTHERAPY

The strategy of maintenance therapy with EGFR-TKIs after first-line treatment has been assessed in several trials. Two phase III trials with molecularly unselected patients have demonstrated that gefitinib was not indicated as a maintenance or an adjuvant therapy in stage III patients after chemoradiotherapy or in patients with completely resected NSCLC [82,83]. In a retrospective study with resected stage I to III pulmonary adenocarcinoma patients harboring *EGFR* exon 19 deletions or exon 21 L858R mutation, a tendency toward improved disease-free survival was discovered in patients receiving adjuvant treatment with gefitinib or erlotinib compared with those who did not receive similar treatment [84]. Nevertheless, additional investigation is warranted to verify the above-mentioned results.

A number of phase III trials in clinically or molecularly unselected patients with advanced NSCLC have also revealed that gefitinib was not indicated for combined treatment with EGFR-TKI and chemotherapy followed by a maintenance therapy with EGFR-TKI alone (Table 2) [45-48]. However, whether an intercalated combination of EGFR-TKI and chemotherapy provides clinical benefit remains debatable [85-87]. Switch maintenance therapy with EGFR-TKIs after first-line chemotherapy has been evaluated in 6 phase III trials (Table 3) [88-94]. In the West Japan Thoracic Oncology Group trial (WJTOG0203), advanced NSCLC patients were randomized to 6 cycles of doublet chemotherapy or 3 cycles of chemotherapy followed by gefitinib until the disease progressed [88]. Significantly improved PFS was observed in the patients receiving chemotherapy followed by gefitinib compared with those receiving chemotherapy alone, although no significant difference in OS was demonstrated. Erlotinib has also been evaluated as a maintenance treatment in the Sequential Tarceva in Unresectable NSCLC (SATURN) trial including 889 molecularly unselected NSCLC patients without progressive disease after doublet chemotherapy for 4 cycles [91]. Erlotinib maintenance therapy yielded significant improvement in PFS (HR: 0.71; $p< 0.0001$), and overall survival compared with placebo (median survival: 12 vs. 11 months; $p = 0.0088$). Similar results were demonstrated in the other studies [92-94].

Similar to the SATURN study, the Iressa in NSCLC for maintenance (INFORM) trial revealed that the gefitinib maintenance therapy provided longer median PFS than placebo (4.8 vs. 2.6 months; $p< 0.0001$), but no significant difference in OS was observed. The PFS of patients receiving gefitinib maintenance therapy was significantly improved in the EGFR-mutant patients (HR: 0.17; 95% CI: 0.07-0.42), but not in EGFR mutation-negative patients (HR: 0.86, 95% CI: 0.48-1.51). In patients with squamous cell carcinoma, no improvement in PFS was also found. The gefitinib maintenance treatment demonstrated a greater benefit in patients with activating *EGFR* mutation [88,91,95].

ADVERSE EFFECTS OF GEFITINIB

The main adverse reactions of gefitinib are dermatologic and gastrointestinal toxicities, including skin rash/acneiform rashes (29-66%), dry skin (15-31%), pruritus (19-45%), paronychia (1-14%), diarrhea (16-47%), and elevated aminotransferase (11-26%) [5,33,35,36,42,76]. Most toxicities were usually mild to moderate. In the IPASS trial, neutropenia (3.7%) and anemia (2.2%) have been reported [5]. Interstitial lung disease (ILD) related to gefitinib has also been observed. An analysis of 50,005 patients initiated by the US FDA revealed that the worldwide incidence of ILD related to gefitinib treatment was approximately 1% [higher in Japan (2%) than in USA (0.3%)], and about one-third of these cases were lethal [96,97]. In a number of recent phase III trial, the reported incidence of ILD ranged from 1.3 to 5.3 % [5,38,40,76]. Gefitinib treatment clearly demonstrated a favorable toxicity profile compared with doublet chemotherapy.

CONCLUSIONS

Gefitinib provides better response rate, improved PFS, and less toxicity compared with platinum-based doublet chemotherapy for advanced NSCLC with activating *EGFR* mutation. Every effort should be made to identify the *EGFR* mutation status before the initial systemic therapy for NSCLC patients. First-line treatment with EGFR-TKI, including gefitinib or erlotinib, should be used in patients with EGFR-mutant advanced NSCLC. For patients with unknown *EGFR* mutation status and poor performance status (PS 3-4), standard chemotherapy is an inappropriate treatment, so EGFR-TKI as first-line therapy could be considered for them. EGFR-mutant NSCLC patients receiving gefitinib had median PFS of approximately 10 months. Further investigations about gefitinib are mandatory in order to develop better treatment strategies and optimal therapy for each patient.

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